

Characterization of Epidemiology Data Relating to  
Prostate Cancer and Exposure to Atrazine

July 17, 2003

Scientific Advisory Panel

## Introduction

The FIFRA Scientific Advisory Panel is being asked to review and consider the Agency's analysis of evidence that exposure to atrazine may be associated with an increased incidence of prostate cancer in humans. The Agency's analysis considers the currently available epidemiology data and largely focuses on a study at a manufacturing plant in Louisiana. This study, initially funded by Ciba-Geigy, later by Novartis, and now by Syngenta, has been updated a number of times over the years as more data on the mortality and incidence of disease have become available. The study was conducted by Dr. Elizabeth Delzell and her colleagues at the University of Alabama. In addition, the Agency's analysis considers a recently published study on prostate cancer results from the Agricultural Health Study (Alavanja et al. 2003) and a correlation analysis of pesticide use and cancer incidence in California counties (Mills 1998).

The National Cancer Institute has a number of other analyses in press or planned which are relevant to atrazine. Among these is a re-analysis of earlier studies involving pesticides and non-Hodgkin's lymphoma using hierarchical techniques to adjust for the effects of multiple exposures. This report is expected to be published online in the next 2-3 months. Further, enough additional prostate cancer cases have been added in the Agricultural Health Study since the recent publication that the analysis can be redone with approximately double the number of cases. Re-analysis is planned later this year and may be ready for publication by next year. An analysis of all the non-Hodgkin's lymphoma cases reported in the Agricultural Health Study is planned to start next year. And a special analysis of all cancers related to atrazine exposure in the same Agricultural Health Study cohort is also planned for this year with publication expected next year. In addition, Syngenta is conducting a nested case-control study of workers at the St. Gabriel plant using more detailed job histories to evaluate exposure indices. This study should be available later this year. Given the importance of incorporating these results into an evaluation of atrazine for prostate cancer and other cancer outcomes, the Agency plans future analyses and absent compelling information in the interim, will wait until all of these analyses are in before addressing the broader question of atrazine exposure and cancer. This paper only addresses currently available information on atrazine and prostate cancer.

## Background

Earlier reviews of atrazine manufacturing plant workers were performed by EPA in 1990, 1994, and 1996. The latest submission by Syngenta, completed October 12, 2001, underwent three reviews at EPA (12/13/01, 3/25/02, and 01/15/03). The first review concluded that it would be appropriate to obtain external peer review comments. Comments were obtained from epidemiologists at the National Cancer Institute (NCI) and Harvard, Dr. Aaron Blair and Dr. Edward Giovannucci, and incorporated into the revised review dated 3/25/02. This review led to a request to Syngenta for additional information concerning the exposure status of the workers at the manufacturing plant. In addition, public comment was received from an expert peer review panel hired by Syngenta and the Natural Resources Defense Council with divergent

interpretations of the study results. A third round of external peer review was conducted including the two original peer reviewers (Drs. Blair and Giovannucci) and two additional reviewers: one from Health and Welfare Canada (Dr. Howard Morrison) and one from the National Cancer Institute (Dr. Richard Hayes). Once the exposure data and the four review comments were received, they were incorporated into the EPA review dated January 15, 2003.

The overall conclusion of the most recent EPA review was that “It appears that most of the increase in prostate cancer incidence at the St. Gabriel plant in Louisiana is likely due to intensive PSA screening. The study was insufficiently large and suffered from other limitations that prevent ruling out atrazine as a potential contributor to the increase observed. On balance, however, a role for atrazine seems unlikely because prostate cancer was found primarily in active employees who received intensive PSA screening, there was no increase in advanced tumors or mortality, and proximity to atrazine manufacturing did not appear to be correlated with risk.”

The key data to be addressed by the Scientific Advisory Panel primarily involve the most recent analysis of incidence at the St. Gabriel manufacturing plant in Louisiana. Workers at the plant received intensive screening for prostate cancer using the Prostate Specific Antigen (PSA) test which increases the ability to detect disease that would not otherwise be identified. Additional data was requested and received concerning the relative exposure status of workers who were diagnosed with prostate cancer. Further, a new Agricultural Health Study has published results germane to determining the risk of prostate cancer among farmers and other applicators who use this herbicide. Each of these studies is addressed in turn below.

### PSA Screening and its Effect on Prostate Cancer Incidence

An epidemiology study was conducted of workers at the Syngenta St. Gabriel plant where atrazine is manufactured (Delzell et al. 2001). That study reported a statistically significant increase in the incidence of prostate cancer among plant workers. The Standardized Incidence Ratio (SIR) ranged from 178 to 255 depending on the comparison population. Workers at the plant received an extraordinarily high rate of PSA screening and reports in the literature suggest that such screening could easily double the detection of prostate cancer (see citations in Adami et al. 2002 and Blondell 2003 including peer review by Dr. Giovannucci). What is not known is whether the PSA screening could explain the entire increase observed in the plant workers, especially those less than 50 years of age. Based on five observed cases, workers in this age group had a prostate cancer incidence that was 6.7 times higher than the Louisiana State population (95% confidence interval was 2.2 to 15.7 times higher) and 4.0 times higher than the nearby industrial corridor (95% confidence interval was 1.3 to 9.3 times higher).

The report from a group of expert scientists (Adami et al. 2002) hired by Syngenta concluded that an apparent 5-fold increase is plausible following systematic widespread screening. The panel pointed out the observed increase is fully compatible with the empirical evidence from outside sources. With respect to the workers in the Syngenta St. Gabriel Plant, the expected

increase among those screened for PSA, many of whom were young and screened repeatedly, would be at least 3 and probably around 3.5 given the young age of those screened and the occurrence of repeated screening on the same individual. Since 92% of the workers had been screened at least once with PSA, the expected incidence of prostate cancer in comparison to the pre-screen incidence would be 3.3 times higher (if A=prostate cancer incidence identified without PSA screening and 92% of the workers have been screened, then prostate cancer detected with screening is  $0.08 \times A + 0.92 \times 3.5 \times A = 3.3 \times A$ ). The ratio of 3.3/1.48 [1.48 is the expected incidence increase in Louisiana due to PSA screening in the general population] equals 2.23, which multiplied by 100 is essentially identical to the SIR estimates for prostate cancer among the workers in the Novartis St. Gabriel Plant (255 with LA state comparison and 178 with industrial corridor comparison). Later, the panel supports the plausibility of a 5-fold increase by citing the Olmstead County, Minnesota study (Roberts et al. 1999) which found a 3.5-fold increase. The panel of expert scientists hired by Syngenta concluded that the “prostate cancer incidence has increased as much as, but no more than, would have been expected . . . There is neither a need to invoke, nor evidence to support, the contribution of environmental factors in the particular occupational setting on prostate carcinogenesis.”

EPA asked four external peer reviewers to comment on the comments and analysis by Adami et al. (2002). One of the external reviewers, Dr. Giovannucci, cited other studies where, in his opinion, PSA screening was responsible for sharp increases in the reported incidence of prostate cancer:

For example, in one study, the ratio of prostate cancer incidence in men who were screened with PSA was 6.5 times higher than the control group. In essence, there were 6.5 times more prostate cancers diagnosed due solely to PSA screening (BJU International 2001;88:811-17). In a screening trial in a Finnish population, the ratio of the number of cases detected through PSA screening in the first year relative to the number expected based on age-specific incidence rate in Finland was 14.4 for men aged 55 years (Cancer Causes and Control 2002;13:279-285). This ratio of screened detected cases to unscreened population incidence increased with age so the potential bias in men aged younger than 55 years would be even greater based on these data. Thus, the increased excess of prostate cancer observed in the Novartis study is compatible with increases expected in a population that is receiving intensive PSA screening.

Note that Dr. Giovannucci finds a greater effect on younger ages because PSA screening detects cases years before the other evidence would make a prostate cancer case evident. Another external peer reviewer, Dr. Blair, agreed that the report by Adami et al. (2002) “suggest[s] that PSA screening may well explain the excess incidence of prostate cancer in this cohort. It would be helpful, however, to have more information supporting the selection of [the] multiplication factor regarding the impact of age and other factors that might differ between a cohort of working individuals and the general population.” The peer reviewers supported the idea that PSA screening was responsible for ascertainment bias resulting in differential detection of prostate cancer in the study and comparison populations. However, they did not all agree that this bias ruled out atrazine as a possible contributor to the excess prostate cancer incidence observed.

### Additional Exposure Analysis of Manufacturing Plant Workers

At EPA's request, Syngenta prepared an atrazine exposure profile of employees diagnosed with prostate cancer. There were 17 cases, including 14 Syngenta cases and 3 contract employees. Exposure information was obtained for 12 of the 14 Syngenta employees. Two of the 14 Syngenta cases did not have the necessary information to classify by exposure but were concluded to have low exposure based upon their job titles. There was no exposure information available for the three prostate cancer cases among contract workers. However, contract workers accounted for 62% of the person years examined and their period of exposure was a median of 2.6 years compared to 20 years for Syngenta employees. These contract employees did not generally receive PSA screening and the incidence of prostate cancer in the contract workers was not significantly higher than the 1.8 cases expected, based on using Louisiana as the comparison population. Using the local industrial corridor as a comparison population, the comparison would be 3 observed prostate cancer cases and 2.7 expected. Therefore, the Agency concludes that the absence of exposure information for contract employees is not of particular concern because the observed number of cases is close to expectation and the duration of exposure to atrazine is relatively low.

Analysis was performed on the 12 of 14 Syngenta cases for which exposure information was available using two methods. First, job titles were obtained from commencement of employment until September 2002 or when employment ended. Jobs were then classified by their "proximity to locations in the plant where atrazine is manufactured, handled, or packaged." Of the 30 different jobs, 5 were classified as remote, 17 were classified as low, 4 were classified as mid, and 4 were classified as high physical proximity to atrazine production. For each case, the proportion of time in each category of exposure was assessed and then cumulated up until the time of prostate cancer diagnosis. For the second method, a relative atrazine proximity scale was developed. Based on atrazine airborne dust monitoring data, remote, low, mid and high proximity areas were found to differ by an order of magnitude. Thus, each category could be assigned a relative exposure factor of 0.1, 1, 10, and 100. This value was multiplied by the duration at each type of location and cumulated to create an index of exposure. This index of exposure was adjusted for reductions in exposure due to changes at the plant in 1984-85.

Results from the method of classifying jobs by proximity found that the 12 cancer cases spent 46% of their plant time in low proximity positions, 26% in medium proximity, and 28% in high proximity to atrazine production. The majority of the high proximity time was due to three of the cancer cases spending the majority of their working time in these positions.

This analysis was supported by the cumulative index of exposure method. Three cases had high proximity to atrazine production throughout their working career at the plant with a cumulative index greater than 10,000. Four cases had a medium exposure with a cumulative index greater than 1,000 and less than 10,000. The remaining five cases had a low exposure index (less than 1,000). As noted above, the two unassessed cases were likely to be low proximity based on their job titles.

Further analysis did not find any relationship between age at diagnosis and proximity to atrazine. Had there been such a relationship, it would have supported the possibility that atrazine was a causative factor in the subsequent diagnosis. At least 12 of the employees with prostate cancer participated in the screening program and 10 of them were initially detected due to the PSA screening. Of the total 14 Syngenta cases, 12 had early stage localized prostate cancer and 2 had regional cancer within the prostate. “No distant, advanced stage, metastasized cancer was detected in Syngenta employees.” Together these results are consistent with the conclusion that the observed significant excess in prostate cancer at the Syngenta plant in Louisiana was more likely an artifact of the extensive PSA screening program than a result of exposure to atrazine.

A major difficulty with the above information was the lack of comparable information for the workers without prostate cancer. This additional information was requested and provided in tabular form, although it was not available to peer reviewers. A copy is provided below:

**Table 1. Estimated Number (%) of Male Employees at St. Gabriel at the End of Each Year (Syngenta Male Employees Only)**

Proximity to Atrazine Manufacturing	Year			
	1977	1986	1996	2002
Low	205 (72%)	275 (77%)	306 (79%)	291 (80%)
Moderate	20 (7%)	20 (6%)	20 (5%)	19 (5%)
High	60 (21%)	60 (17%)	63 (16%)	55 (15%)
Total Number	285	355	389	365

Based on this Table, an average of 77% of Syngenta employees had low proximity to atrazine manufacturing; an average of 6% had moderate proximity; and 17% had high proximity to atrazine manufacturing. Of the 14 prostate cancer cases, 50% were classified as low proximity to atrazine manufacturing, 28% were classified as moderate proximity, and 21% were classified as high proximity. It appears that there would be no strong evidence of dose-response, although a higher proportion of diagnosed workers (50% versus 23%) were involved in jobs with moderate or high proximity to atrazine manufacturing. Chi-square tests performed by Breckenridge (2003) found a higher than expected incidence of prostate cancer cases was distributed to the moderate proximity subgroup. EPA determined that no strong conclusions should be drawn from this crude comparison. A proper comparison would require measuring the exposure of cases and non-cases in the same manner and taking into account confounders such as age and person-years of exposure. Syngenta acknowledges this shortcoming and is planning a case-control study within the cohort to address this issue. External peer reviewers only had access to the exposure categorization of the prostate cancer cases, not the other plant workers. So their conclusions were limited because they could not examine the data presented above.

### New Results from Agricultural Health Study in Iowa and North Carolina

Tied into the assessment of atrazine and prostate cancer is the recently published study Alavanja et al. (2003). This large prospective cohort study of 55,332 male pesticide applicators, known as the Agricultural Health Study, reported on the risk of prostate cancer and computed odds ratios for individual pesticides within the cohort. Results for atrazine, presented in Table 5, reported an odds ratio of 0.94 for ever/never use reported by questionnaire with a 95% confidence interval of 0.78 to 1.14. The Agricultural Health Study has a number of advantages over other epidemiologic studies of pesticides. It is the largest study of its kind, determines exposure prior to disease (thus, eliminating recall bias), analyzes a wide variety of potential and known confounders including other pesticide exposures, and has greater statistical power to detect small effects. Given the relatively tight confidence interval and based on this study alone, the Agency concludes that atrazine is an unlikely cause of prostate cancer among farmers. Seasonal exposure among commercial and private applicators in the Agricultural Health Study is very different from the year round exposure in the Delzell et al. study described above. On the one hand intensity of exposure in an uncontrolled agricultural environment may be greater for certain individuals (e.g., exposed to spill or hose break without personal protective equipment), but the duration of exposure (days per year) is considerably less. This raises the question about the ability to compare workers in the field versus workers in a manufacturing plant which the Agency is asking the Scientific Advisory Panel to address.

### Correlational analysis of pesticide use data and cancer incidence in California counties

California has maintained a population-based cancer registry since 1988 and a state-wide pesticide use reporting system. Mills (1998) obtained 1993 pesticide usage data for six pesticides with a suspicion of carcinogenicity based on other toxicologic and epidemiologic studies. These data were compared using regression analysis with county age- and race- adjusted cancer incidence rates (1988-92). A borderline statistically significant correlation was found between atrazine usage and prostate cancer in black males. This study is subject to aggregation bias because exposure of individuals in the county were not measured. EPA considers such studies useful for guiding future studies, but not for reaching conclusions about causation.

Table 2 below summarizes the pertinent epidemiologic studies relating prostate cancer and atrazine exposure. The table includes a new study by Mills and Yang (2003) which was not considered in this background paper because it did not consider exposure to atrazine. However, it is included in the table because its result may affect the Scientific Advisory Panel's interpretation of the Mills (1998) study. The later study by Mills and Yang (2003) did not include atrazine as one of the chemicals for analysis. This suggests that the authors did not consider the earlier finding strong enough to warrant follow-up or, perhaps, the relatively low usage of atrazine in California was insufficient for the more detailed analysis employed in their later study.

**Table 2. Summary of epidemiologic studies related to atrazine and prostate cancer**

Reference, location	Subjects	Exposure contrast	SIR* or OR* (95% CI)
Alavanja et al. 2003, Iowa, North Carolina	364 cases with use 202 never used	ever exposed to atrazine versus never exposed (cohort 55,332)	OR = 0.9 (0.8-1.1)
Delzell et al. 2001, LA manuf. plant	757 plant workers screened for PSA	plant worker incidence compared to Louisiana State	<b>SIR = 255**</b> <b>(148-408)</b>
same as above	same as above	plant worker incidence compared to industrial corridor	<b>SIR = 178</b> <b>(104-285)</b>
Mills and Yang 2003, California***	222 cases 1110 controls	high area use of <u>simazine</u> versus low use (atrazine not measured)	<b>OR = 1.5</b> <b>(1.02-2.3)</b>
Mills 1998, California	geographic analysis by county	significant correlation between prostate cancer in Black males and atrazine use by county	<b>r = 0.67</b> <b>(CI = .01-.97)</b>

\* SIR = Standardized Incidence Ratio, OR = Odds Ratio.

\*\* **Statistically significant findings in bold type.**

\*\*\* This study is provided because it is a follow-up to the earlier Mills 1998 study.

## Conclusion

EPA concludes that the available data do not support a likely relationship between atrazine exposure and prostate cancer. It appears that most of the apparent increase in prostate cancer incidence at the St. Gabriel plant in Louisiana is likely due to more complete detection through intensive PSA screening. The study was insufficiently large, which prevented more detailed analyses that could have better defined the relationships between exposure and disease. The study suffered from lack of careful assessment of exposure in cases and comparison populations. These limitations prevent ruling out atrazine as a potential contributor to the increase observed. On balance, however, a role for atrazine seems unlikely because prostate cancer was found primarily in active employees who received intensive PSA screening, there was no increase in advanced tumors or mortality, and proximity to atrazine manufacturing did not appear to be correlated with risk. The Agricultural Health Study did have sufficient power but did not find an association between atrazine use among agricultural applicators in Iowa and North Carolina and incidence of prostate cancer.

This background paper is based primarily on EPA's "Review of Additional Data on Potential Atrazine Exposure and Review Comments Submitted by Syngenta and NRDC on the Atrazine Cancer Epidemiology Study" (Blondell 2003). This complete 16 page review should be used by the Scientific Advisory Panel as a primary document stating the Agency's position. Attached to the 16 page review are copies of all four external peer reviews.



### **Epidemiologic studies and reviews relevant to prostate cancer and atrazine**

Alavanja MCR, Samanic C, Dosemeci M, et al. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol* 157:800-814.

Breckenridge CB. 2002. Summary of information on potential atrazine exposure for 12 out of 17 prostate cancer cases reported by Delzell et al. 2001. Nov. 1, 2002. [?? resolve confidentiality]

Breckenridge C. Jan. 16th and 17<sup>th</sup>, 2003. St. Gabriel Workforce: male Syngenta Employees excluding contract manufacturers. Two Emails to Jerry Blondell with Attached Table.

Delzell E, et al. 2001. Cancer Incidence Among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant” Oct. 12, 2001. MRID# 451521-01 and 455184-01, Chemical #080803. [Technical Report 170 pp.]

MacLennan PA, Delzell E, Sathiakumar N, et al. 2002. Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med.* 44:1048-1058.

MacLennan PA, Delzell E, Sathiakumar N, et al. 2003. Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A* 66(6):501-517.

Mills PK, Yang R. Prostate cancer risk in California farm workers. 2003. *J Occup Environ Med.* 45:249-258.

Mills PK. 1998. Correlation analysis of pesticide use data and cancer incidence rates in California counties. *Arch Environ Health.* 53:410-3. [also relevant to other cancers]

### **Review comments on the above studies**

Adami H, Colditz G, Mandel J, Trichopoulos D. 2002. An evaluation of the report by Dr. Delzell et al., 2001 on “A follow-up study of cancer incidence among workers in triazine operations at the Novartis St. Gabriel plant”. July 2002.

Blondell J. Jan. 15, 2003. Review of Additional Data on Potential Atrazine Exposure and Review Comments Submitted by Syngenta and NRDC on Atrazine Cancer Epidemiology Study: “Follow-up Study of Cancer Incidence Among Workers in Triazine-related Operations at the Novartis St. Gabriel Plant” by Elizabeth Delzell et al. DP Barcode D287278, MRID# 455184-01, Chemical #080803. Includes attached are external peer review comments by Dr. Howard Morrison, Health and Welfare Canada (12/23/02), Dr. Edward Giovannucci, Harvard School of Public Health (12/31/02), Dr. Richard Hayes, National Cancer Institute (1/8/03), and Dr. Aaron Blair, National Cancer Institute (12/23/03).

Natural Resources Defense Council. 2003. Comments on the Atrazine IRED. May 5, 2003.

**Questions for the Science Advisory Panel**

1. After reviewing the study of manufacturing workers at the Syngenta St. Gabriel plant; the comments of EPA external peer reviewers; and public comments from the Syngenta sponsored peer review and the Natural Resources Defense Council, and the supplemental exposure analysis conducted for the St. Gabriel plant workers, EPA has concluded that the increase in prostate cancer observed in the St. Gabriel manufacturing plant workers could be explained by the increase in PSA screening for these workers. Due to lack of detailed exposure analysis based on job history and the limited statistical power due to small sample size, atrazine could not be ruled out as a potential cause but a role for atrazine seems unlikely. Please comment on EPA's conclusion. Please identify any additional data or analyses of the St. Gabriel cohort that the Agency should consider before reaching a final conclusion.
  
2. Other available studies may assist the assessment of the potential for association between atrazine exposure and prostate cancer. Agricultural workers generally have much shorter duration of exposure compared to workers at a manufacturing plant. In addition, agricultural workers are expected to have a different pattern of exposure compared to manufacturing workers (e.g., intensity, seasonality, routes of exposure). Please comment on comparing the results of the epidemiology study of prostate cancer conducted in the St. Gabriel plant to the results of the Agricultural Health Study, considering that the participants in these two studies were likely to have experienced different exposures. Discuss what such a comparison indicates about a relationship between exposure to atrazine and prostate cancer.